FDA CASE STUDY

A start-up company investigates marketing pathways for a unique pediatric device

REGULATORY PATHWAYS FOR PEDIATRIC MEDICAL DEVICES: MARKETING A PEDIATRIC MEDICAL DEVICE VIA A HUMANITARIAN DEVICE EXEMPTION

THIS FICTIONALIZED CASE STUDY IS THE FOURTH IN AN EDUCATIONAL SERIES PUBLISHED BY THE U.S. FOOD AND DRUG ADMINISTRATION.

Realizing Childhood Dreams

"Good Morning!" Cynthia Versetz called out cheerfully as she walked into the offices of Pediatric Hope, LLC., (PHL). The three-person medical device start-up company begun by business partners Dr. Peter Stewarth and Dr. Ivan "Sparky" Marse had just started renting the small office space and there were still boxes tucked into corners. Versetz was a recent business school graduate who had a special interest in the medical device market. She counted herself lucky to have found a job right out of school in her field of interest.

"Good morning," the men called out as she took a seat at her desk. Logging into her computer, she could hear the two talking in Marse's office. Dr. Marse was a renowned computational fluid dynamics researcher who had retired from the National Aeronautics and Space Administration's (NASA) Advanced Supercomputing Division a few years ago. Dr. Stewarth, also retired, was a pediatric cardiac surgeon with many patents to his name. Childhood friends, both doctors had lost young family members to heart disease. Those experiences fueled their dream of collaborating to make a significant impact on the world: the creation of a miniaturized heart pump with rhythm and synchronized pacing control called the PHL System, a pediatric, life-saving device.

An implant with an external support system, the PHL device was designed to treat pediatric restrictive cardiomyopathy, a diseased state of the heart involving abnormalities of the muscle fibers that affect blood flow (Appendix A). The device can also prolong the waiting period for patients on the heart transplantation list. It consists of three components:

- Implantable Miniature Pump (IMP): A continuous flow pump that assists the heart in transporting blood from either the right ventricle to the pulmonary artery or from the left ventricle to the aorta.
- Cardiac Rhythm and Pacing Controller (RPC): An electrical stimulator that assists in maintaining a normal heart rhythm.
- Energy Distribution Pack (EDP): External power supply necessary to run the system.

While the IMP and the leads of the RPC are implantable parts, the remaining hardware and accessories can be packaged inside a small, fashionable backpack that is external to the patient. (Appendix B)

Giving Hope To Children With Heart Diseases

After printing out her research, Versetz joined the doctors in Marse's office. Her job was to help formulate PHL's business plan and regulatory strategy. Handing the papers to Stewarth and Marse, Versetz began.

"According to the Pediatric Cardiomyopathy Registry, 1 in every 100,000 children in the United States under the age of 18 is diagnosed with cardiomyopathy. There are four types: dilated, hypertrophic, restrictive, and miscellaneous.

Current treatments of cardiomyopathy include medical and pacing therapies, surgical options, cardiac assist devices (mechanical hearts), and heart

transplantation. Our device provides both pacing therapies and cardiac assistance for the heart."

"Thanks for gathering this research, Cynthia," Marse said. "Have you found out anything about the regulatory process we'll need to get the PHL System to market?"

"I did!" she replied. "There are a number of possible indications for use for the PHL System. According to a guidance document I found on the Food and Drug Administration (FDA) Web site called "Premarket Assessment of Pediatric Medical Devices," we'll really need to narrow that down. We might want to consider just indicating our device for pediatric patients who suffer from restrictive cardiomyopathy since the design of our device is so unique for that disease.

"While digging around the FDA site I found a page on Humanitarian Device Exemption (HDE), a regulatory pathway available to devices that target rare diseases or conditions," Versetz continued. "We could pursue the HDE if the FDA determines the PHL System is a Humanitarian Use Device (HUD). HUDs are devices that are intended to benefit patients being treated for or diagnosed with a disease or condition affecting fewer than 4,000 individuals in the U.S. per year. However, we will need to explain to the FDA why our device can only treat pediatric restrictive cardiomyopathy patients. The Office of Orphan Products Development (OOPD) within the FDA generally designates devices as HUDs based upon aspects of the disease or condition relevant to the functionality of the device. The OOPD will consider how the device works to treat the disease and if we are unable to explain why the device should be limited to pediatric restrictive cardiomyopathy patients, then we may not be able to pursue this marketing pathway. That is because FDA might consider the device to benefit a broader disease such as pediatric cardiomyopathy in general and that entire population may not qualify since the annual incidence of new patients with that disease exceeds the statutory limit of 4,000 patients per year. But given that we believe our device is unique for only pediatric restrictive cardiomyopathy, we might be able to pursue the HUD/HDE pathway."

The doctors were impressed by their young associate's suggestions. "Great job, Cynthia! This is a very interesting approach, one definitely worth investigating," said Marse.

"I am curious to know what other regulatory pathways to commercialization might be open to us for the PHL System," Stewarth said. "Could you brief us on other options?"

"Not well, I'm afraid," Versetz replied. "Though I've read enough about regulatory pathways to make my eyes cross over the past week, I'm definitely no expert. Luckily, the FDA has established a Pediatric Device Consortia (PDC) program that awards grants to groups that serve as resources to companies like us that have ideas for medical devices that can advance the health and well-being of children. I can reach out to the consortia groups that have been awarded grants by FDA after this to get us a meeting with one of their experts so we can discuss regulatory pathways for the PHL System in more detail."

"Perfect, let's do it!" Marse exclaimed happily. Stewarth nodded in agreement.

Versetz left the office to call one of the PDC grantees right away.

HDE Versus Other Regulatory Pathways

The following week, the employees of Pediatric Hope met with Dr. Pepper Laws, an attorney with extensive expertise in regulatory affairs who worked at one of the PDC groups awarded a grant by FDA. "Well, it is very nice to meet you all," said Laws as the group settled in her office. "Cynthia filled me in via E-mail on the general details of why you are here, so let's start this meeting off with some specifics. What is the intended use of your device and are there any unique characteristics of the PHL System that I should be aware of?"

Marse jumped in. "The PHL System is a miniature heart pump with synchronized pacing control that provides ventricular tachycardia therapy and pumps blood from the left ventricle of the heart

Exhibit 1. The Pediatric Device Consortia Grant Program

The PDC Grant Program was created by the Food and Drug Administration Amendments Act of 2007 (FDAAA) to provide advisory services to innovators of medical devices for children. The goal of the FDA's PDC Grant Program is to support the development of nonprofit organizations designed to stimulate projects that will promote pediatric device development.

The PDC facilitate the development, production, and distribution of pediatric medical devices by:

1. Encouraging innovation and connecting qualified individuals with pediatric device ideas with potential manufacturers
2. Mentoring and managing pediatric device projects through the development process, including product identification, prototype design, device development, and marketing
3. Connecting innovators and physicians to existing Federal and non-Federal resources
4. Assessing the scientific and medical merit of proposed pediatric device projects
5. Providing assistance and advice as needed on business development, personnel training, prototype development, and post-marketing needs

throughout the bodies of pediatric patients suffering from restrictive cardiomyopathy. The device design is different from any other type of mechanical heart pump being developed or on the market and is unique only to pediatric patients with restrictive cardiomyopathy. This unique design does not allow it to be used outside of this disease."

"Thank you," Laws replied. "Now while I'm sure you were trying to keep your explanation simple for me, I suggest we make your description for the intended use of the device to be a little more specific concerning your target population. Beyond describing them generally as 'pediatric patients,' I recommend specifying relevant age subsets of the pediatric population in your intended use and indications for use statements that you include in your paperwork for FDA. (Table 1)

"For example, you should identify the specific pediatric subpopulation that you intend to treat by age and/or weight," Laws continued. "You should also include the factors and characteristics laid out in FDA's Guidance on Premarket Assessment of Pediatric Medical Devices, with respect to your device design, clinical study design, and labeling for each population, especially unique issues that may arise when used in your targeted pediatric population. This will help FDA better understand the intended patient population for your device."

"We can do that," said Versetz. Marse and Stewarth nodded in agreement.

"Good. Now, you mentioned that your device will treat restrictive cardiomyopathy. Will it treat other types as well? That would also be important information for you to include in your indications for use."

Seeing an opportunity to have his questions answered, Stewarth responded. "That is actually one of the main reasons we've come here today. There are four types of cardiomyopathy, and as we have mentioned, our device can only be used for treating pediatric restrictive cardiomyopathy. When we were discussing this in our office, Cynthia mentioned that we might be able to qualify for the HUD/HDE pathway because our device design treats only pediatric patients with restrictive cardiomyopathy, which is a small patient population. Our device has a special feature that limits it to only that disease, so the device would be inappropriate to be used in any other type of pediatric cardiomyopathy patient. We understand from reading the

Table 1: Approximate Age Range of Pediatric Population Subgroups

Pediatric Subgroup: Approximate Age Range
Neonate: birth through 1 month of age
Infant: greater than 1 month of age to 2 years of age
Child: greater than 2 years of age to 12 years of age
Adolescent: greater than 12 years of age through 21 years of age (i.e., through last day before the 22nd birthday)

Note: The Guidance on Premarket Assessment of Pediatric Medical Devices further clarifies the subgroups as noted. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089742.pdf

'Guidance for Humanitarian Use Device Designations' that this is known as 'orphan subset'."

Pleased, Laws turned to the young woman. "I'm impressed by your knowledge of regulatory affairs Cynthia."

Returning her attention to Stewarth, the attorney continued. "Yes, Dr. Stewarth, an HDE might be an option to apply for, but first the PHL System must be designated as a HUD. Since the device design limits it to treating only pediatric restrictive cardiomyopathy, you will need to explain to OOPD why the device cannot be used outside of that disease and that pediatric restrictive cardiomyopathy occurs in less than 4,000 new patients per year in order to be designated as a HUD. You should also be aware that there are restrictions on the profits you can obtain if you market your device via an HDE, though there are some exemptions that may apply if your device is approved and labeled for pediatric patients."

"Well, we aren't specifically trying to make a return on the investment with the PHL System, but I admit I'm a bit concerned," replied Stewarth.

Marse agreed. "It seems like a market size of less than 4,000 would prevent us from recovering even our developmental costs. Even though I just retired, I only recently paid off my loans from medical school!"

"I understand your concern," Laws chuckled. "But let me explain a bit more about the HUD/HDE process so you that have a better understanding of what this will entail.

"On November 3, 1998, FDA issued a final rule to carry out provisions of the Safe Medical Devices Act of 1990 regarding HUDs[1] by defining them as devices intended to benefit patients by treating or diagnosing a disease or condition affecting fewer than 4,000 individuals in the U.S. per year. Under the statute, the amount charged by a manufacturer could not exceed the costs of the device's research, development, fabrication, and distribution, making production of these types of devices a truly humanitarian endeavor. FDA, in turn, created regulations to implement the statute for the development of devices used in the treatment or diagnosis of diseases affecting populations impacted by rare diseases. Once your device has been designated as a HUD by OOPD, you are then eligible to submit an HDE marketing application to either the Center for Devices and Radiological Health (CDRH) or to the Center for Biologics Evaluation and Research[2]. For your device, you'd be submitting the HDE to CDRH. Devices that pursue the HDE marketing application are exempt from having to meet the effectiveness requirements of

[1]Humanitarian Use Device (HUD) Designation

http://www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseases Conditions/DesignatingHumanitarianUse DevicesHUDS/LegislationRelatingto HUDsHDEs/UCM336515.pdf

[2]Note: A Draft Guidance is subject to change and is not for implementation. Humanitarian Device Exemption (HDE): Questions and Answers—Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationand Guidance/GuidanceDocuments/UCM389275.pdf

sections 514 and 515 of the Federal Food, Drug, and Cosmetic (FD&C) Act as authorized by section 520(m)(2).

"Good to know," Marse replied. "But I feel like we've just spent a lot of time focusing on the HUD/HDE route," said Stewarth. "Are there any alternative regulatory pathways you could tell us about?"

"Of course," Laws said. "To begin, you could request a determination by FDA if your device is a significant risk or non-significant risk device or you could identify and work with an established Institutional Review Board (IRB) to make that determination, but ultimately FDA makes the final decision. Since the PHL System is a life-sustaining implant, the FDA will certainly find it to be a significant risk device. In this case, you would need to satisfy all Investigational Device Exemption (IDE) requirements in order to conduct a clinical study.

An IDE allows the investigational device to be used in a clinical study in the United States in order to collect data required to support a premarket submission. Now, there are four regulatory pathways that are available to medical devices: Premarket Approval (PMA), *de novo* classification, Premarket Notification [510(k)], and HDE."

"A device with an approved PMA is approved for marketing based on valid scientific evidence and reasonable assurance that the device is safe and effective for its intended use. It is the most stringent route as you'd have to perform clinical trials before your device could be deemed safe and effective. In contrast, a 510(k) device is cleared for marketing when FDA finds that it is at least as safe and effective—in other words, substantially equivalent—to a legally marketed predicate device that is not required to have a PMA. With this route, you are typically required to do testing to demonstrate that your device is substantially equivalent, in safety and effectiveness, to the predicate device."

"So if it's easier and will save us money, why shouldn't we aim for the 510(k) route for our PHL System?" Marse asked.

"Well, I did a little digging before you came using the preliminary information Cynthia sent me," responded Laws. "According to the FDA Center for Devices and Radiological Health (CDRH) Product Classification Database, your PHL System seems to be very similar to three product classes: the Implantable Pulse Generator with Cardiac Resynchronization (Product Code: NKE), the Pediatric Ventricular Assist Device (Product Code: PCK), and the Temporary Cardiac Support Blood Pump (Product Code: PBL). These are all Class III medical devices and generally require PMA for approval, so you cannot go the 510(k) or *de novo* route. Realistically, you have two options due to the classification of your device: the PMA or the HDE."

Versetz had been taking notes, but paused to ask a question. "Dr. Laws, could you give us more information about HDEs and explain the differences between the HDE and PMA pathways a bit more?"
"Sure. As I said, once your device has been designated as a HUD by OOPD, you are eligible to submit the HDE marketing application. The HDE is similar in both form and content to a PMA application, but is not necessarily required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. Rather, the HDE application must contain sufficient information and data for FDA to determine that:

1. The device does not expose patients to an unreasonable or significant risk of illness or injury.

2. The probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

3. In addition, to be eligible for HDE approval, FDA must determine that the device would not be available to a person with the disease or illness in question without the HDE approval and that there is no comparable device, other than another device approved under an HDE or Investigational Device Exemption (IDE), available to treat or diagnose the disease or condition.

"An approved HDE authorizes marketing of the HUD and the labeling for a HUD must state that the device is a humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated.

"And before I forget, if you were still concerned about the financial impact of pursuing a HUD designation and device exemption, Section 303 of the Pediatric Medical Device Safety and Improvement Act (PMDSIA) of 2007 opens up former profit restrictions for HUDs and subsequent legislation under the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012 further expanded the profit restrictions. The new criteria to allow a HUD to be exempt from the profit restrictions are:

1. The device is intended for the treatment or diagnosis of a disease or condition that occurs in pediatric patients or in a pediatric subpopulation, and such a device is labeled for use in pediatric patients or in a pediatric subpopulation in which the disease or condition occurs; or

2. The device is intended for the treatment or diagnosis of a disease or condition that does not occur in pediatric patients or that occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe.[3]

If an HDE-approved device does not meet either of the eligibility criteria as determined by FDA, then the HUD cannot be sold for profit. Furthermore, the legislation states that if a HUD meets the eligibility criteria and FDA agrees, the manufacturer is permitted to sell the HUD for profit as long as the number of devices distributed in any calendar year does not exceed the Annual Distribution Number (ADN). The ADN is defined as the number of devices reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States. This can be thought of as the number of devices per year reasonably needed to treat, diagnose, or cure an individual and multiplying that value by 4,000. So if an individual needs two devices in a calendar year, then the ADN would be calculated to be 8,000 and the manufacturer could sell the device for profit as long as they didn't distribute more than 8,000 devices. Once the 8,000 value is exceeded, the manufacturer can only sell the device at the amount that doesn't exceed the costs of the device's research, development, fabrication, and distribution.

"So, pursuing a HUD designation and an HDE for the PHL System is certainly a valid option for you to consider. Note that even after the HDE is approved for the disease or condition, there is still some ongoing oversight and involvement by an IRB as well as FDA's post-approval requirements. IRB approval is required before an approved HUD can be used at a facility."

Pausing to take a sip of water, Laws smiled at the employees of PHL, who looked slightly overwhelmed. "Well, I think we've covered a lot of ground today. Before we end, let me give you something." Laws passed out another printout. "I've summarized some elements of the four regulatory pathways available for medical devices in this table for you to compare (Table 2). Take some time to research the requirements of the regulatory pathways and digest what we have discussed today. We can talk about how to proceed with the pathway you choose for your venture in a few weeks."

[3]Humanitarian Device Exemption (HDE): Questions and Answers, http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm389154.htm

Table 2: Some Elements to Consider When Choosing Your Regulatory Path

Element	510(k)	*De Novo*	PMA	HDE[1]
Submission Fees[2]	~$5,000[3]	$0	~$260,000[3]	$0
Target Review Time	90 Days	120 Days	180 Days	75 Days
Profit	Allowed	Allowed	Allowed	Allowed in certain circumstances[4]

[1]*HDE Regulations: Questions and Answers, Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff, p. 5. Available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM389275.pdf*

[2]*2014 Medical Device User Fee http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm363664.htm*

[3]*The fees associated for a small business and/or a first time submission might be reduced or waived. (See 2014 Medical Device User Fees.)*

[4]*HDE Regulation: Questions and Answers, pg. 4*

"Thank you very much, Dr. Laws. This was really helpful," said Versetz. After exchanging handshakes, the members of PHL returned to their office. They had a lot of thinking to do.

Meeting Unmet Medical Needs

After a quick lunch, Marse, Stewarth, and Versetz reconvened.

"Based on everything we learned today about the regulatory pathways for medical devices, what should our next move for the PHL System be?" Versetz asked the doctors.

After taking some time to think, Marse responded. "Giving hope to pediatric heart patients and their families is our company's vision. Our regulatory strategy should depend on our business values and objectives. Financial profit is not our only motivation to produce the PHL System. I certainly would like to see our product fulfill an unmet medical need in a timely manner; and, particularly, help those who are vulnerable and disadvantaged because of the lack of incentives to research and treat such diseases. What do you say, Pete?"

Stewarth nodded. "I think you're right, Sparky. It might not make us rich, but I think pursuing a HUD designation and obtaining an HDE is the correct path for our company to take. We would help children in need by providing a bridge to transplant or a destination therapy for children with restrictive cardiomyopathy."

Cynthia nodded. She knew she had made the right decision joining this company. "Great," she said. "I'll let Dr. Laws know our decision right away. We'll need more advice from her on what to do to get the PHL System designated as a HUD so we can apply for the HDE."

Obtaining a HUD Designation and HDE Approval

A few weeks later, the PHL team was back at the PDC grantee's office.

"Hello again," Laws greeted the trio. "I was so excited to hear that you were interested in pursuing the HUD/HDE pathway! I wanted to wait a few weeks before we met so that we could make sure we had everything in order before we spoke. I've been in touch with Cynthia about a few questions, so let's see where we are at with those answers."

Laws turned to Marse and Stewarth. "As I've explained to Cynthia, after

our last meeting I was concerned about the PHL System's eligibility to apply for a HUD and subsequent HDE.

According to section 520(m)(2)(B) of the FD&C Act, the FDA cannot approve an HDE for a HUD device when a comparable device, other than another device approved under an HDE or Investigational Device Exemption (IDE) [21 CFR Part 814.104(b)(2)], is available to treat or diagnose the disease or condition. You'll need to make sure that the PHL System meets these criteria to be eligible for HDE consideration."

"Not to worry, Dr. Laws," Versetz stated confidently. "After our meeting, we researched the product codes for the three devices on the market that you said were similar to ours: the Implantable Pulse Generator with Cardiac Resynchronization, the Pediatric Ventricular Assist Device, and the Temporary Cardiac Support Blood Pump. All of these are Class III medical devices that have been approved through the PMA pathway, but our PHL System is very unique. Our device will focus on treating pediatric restrictive cardiomyopathy by providing both pacing and blood flow. Because of those features, we have a unique device design. We have not found any comparable device on the market that is able to treat the disease."

"Then it sounds like the PHL System is novel enough. Great job," said Laws. "Okay then, on to the two-part HDE approval process[4].

[4]4GAO-12-225 Report on Pediatric Medical Device, December, 2011, pp. 8-9 http://www.gao.gov/assets/590/587164.pdf

"First, the PHL System must obtain HUD designation from FDA's OOPD. You'll have to provide them with the scientific rationale supporting use of the device for the rare disease or condition and documentation to demonstrate that the patient population for the orphan subset of pediatric restrictive cardiomyopathy, as we had discussed previously, occurs in fewer than 4,000 new patients per year to justify your HUD designation. If a HUD designation is granted, you can submit an HDE application [21 CFR Part 814.104(b)(1)]. Be aware that while receiving a HUD designation is a prerequisite for submitting an HDE marketing application, it does not guarantee the ultimate approval of the HDE. Here's a sheet with more details on the HUD application," she said, handing papers to the group (Table 3).

Table 3. Information for HUD Designation Application

Application Requirement	Requirement Description
Description of the Disease or Condition	Proposed disease or condition that will be treated or diagnosed by the device.
Scientific Rationale	1. Describe the disease or condition 2. Explain why pacing and external blood pump are needed 3. Expound on the science of the PHL System that treats pediatric restrictive cardiomyopathy and how the special features of the device limit the use to only pediatric restrictive cardiomyopathy
Population Estimate for the HUD population	1. Describe the challenges of the pediatric population with restrictive cardiomyopathy 2. Demonstrate that the PHL System patient population meets the definition of 21 CFR Part 814.3(n); i.e., present data to support that there are fewer than 4,000 U.S. pediatric patients with pediatric restrictive cardiomyopathy 3. Cite supporting literature, research reports, etc.

"Thank you," said Marse. "So after we apply and receive a HUD designation, what would be the next steps for acquiring an HDE?"

"For HDE approval, you need to focus on demonstrating the safety and probable benefit[5] of the PHL System and the lack of a comparable device on the market," said Laws.

"Fortunately, there is no user fee for HDE applications under the Medical Device User Fee and Modernization Act of 2002[6], as reauthorized and amended by the Medical Device User Fee Amendments of 2012, so that is one less development expense for you to worry about Dr. Stewarth."

While the group laughed, Laws handed them another printout with a table breaking down the components of the HDE application (Exhibit 2). "As you can see in this list, the HDE application contains a significant amount of material, including data from preclinical and clinical studies. Perhaps I should spend the rest of our time describing these studies and the data requirements and a number of the caveats you'll encounter since your device will deal with pediatric patients."

Exhibit 2. List of Information for the HDE Application

1. FDA's HUD designation letter
2. A statement indicating that the device is a humanitarian use device*
3. Indication for use
4. Device description
5. Evidence (data) demonstrating device safety
   - a. Preclinical studies
     - i. Bench tests (in vitro)
       - Component, Sub-system and System
       - Reliability and Shelf-Life
       - Biocompatibility and Sterilization
     - ii. Animal tests (in vivo)
   - b. Clinical studies
     - i. Study Design Considerations
       - Therapeutic/Diagnostic Objectives
       - Targeted Patient Population
       - Clinical Protocol
     - ii. Study Results
   - c. Summary of Safety and Probable Benefits
6. A rationale and data supporting the probable benefit of the device

**Note: The HDE device label must include the following statement: "Humanitarian Device. Authorized by Federal law for use in the (treatment or diagnosis) of (specify disease or condition). The effectiveness of this device for this use has not been demonstrated."*

Source: "HDE Checklist for Filing Decisions." Available at:

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/ucm056830.pdf

Demonstrating the Safety and Probable Benefit of the PHL System for HDE approval

Laws began by explaining the general principles of medical device evaluation. "In general, FDA assesses safety and effectiveness—or in your case since you are pursuing an HDE, probable benefit—of all devices no matter if they are intended for the pediatric or adult population[7].

[5]Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf

[6]See 21 U.S.C. § 379j(a)(2)(B)(i).

[7]Premarket Assessment of Pediatric Medical Devices, pp. 5-6

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089742.pdf

Device considerations you'll need to consider include, but are not limited to, the following preclinical and clinical testing as well as other regulatory controls:

- Biocompatibility, including toxicity and carcinogenicity
- Sterility and infection control
- Environmental factors related to location of use, such as electromagnetic fields and radiation
- Human factors such as ease of use and alarm signal effectiveness
- Design controls and the Quality System Regulation

"In some cases where FDA may require that a manufacturer obtain clinical data to support the HDE marketing application, the manufacturer will need to obtain an Investigational Device Exemption (IDE) from FDA. An IDE allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated. To protect the safety of study subjects there are some requirements that need to be met:

- An investigational plan approved by an IRB. If the study involves a significant risk device, the IDE must also be approved by FDA.
- Informed consent from all patients
- Labeling stating that the device is for investigational use only
- Monitoring of the study
- Required records and reports

"Because the pediatric population represents a particularly vulnerable group, specific measures are needed to protect the safety of pediatric study subjects. Adult devices may be inappropriate for use in pediatric subjects for many reasons, or may require specific design changes and/or specific labeling to accommodate their use in pediatric subjects. When developing devices or planning a clinical trial for devices intended for pediatric subjects, I always recommend including these considerations:

- Height, weight, and body surface area
- Childhood growth and development (How the device impacts the child and how these realities impact the device over time—will it need to be replaced or can it grow with the child? Is the device able to withstand the activity level of a growing child?)
- Specific pediatric disease conditions and hormonal influences
- How potential neurologic, immune, anatomical, and physiologic factors may differ from an adult

"FDA is committed to following the least burdensome principles as described in the guidance 'The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles.' This commitment applies equally to pediatric devices. As potential sponsors of pediatric device clinical trials or any device clinical trials, you should take advantage of Pre-Submission meetings with the relevant FDA review division to foster relations, obtain feedback on the PHL System's investigational protocol before initiating the trial to collect clinical data to demonstrate that the device meets the regulatory threshold of safety and probable benefit, and to discuss the least burdensome regulatory path."

Versetz looked at her bosses. "I'll find out what division within CDRH we'll need to contact. We should initiate a discussion with the FDA soon." The men nodded.

Laws continued, "Before your device proceeds to clinical studies, you'll need to prepare for preclinical testing. FDA may request bench or animal data depending on the type of device, the target population, and the extent of existing knowledge about the device to demonstrate that the device performs as designed. In many cases, FDA has developed device-specific guidance documents that will provide information on the types of preclinical testing that should be completed either to support marketing or the initiation of a clinical trial. Again, I recommend contacting the reviewing division and visiting the

CDRH Web site for a complete listing of guidance documents relevant to your device. The classification of Class III of the PHL System will determine the appropriate degree of necessary controls and valid scientific evidence, and help direct you to the relevant guidance documents for your device."

Laws continued. "Furthermore, the HDE submission will need to contain the design concepts and your strategy for evaluating the device. In formulating your strategy, you must adhere to the applicable regulatory requirements appropriate for the risk classification of the device (Class III). You should also consider the following common regulatory requirements: nonclinical studies of in vitro bench testing [21 CFR Part 58(d and e)], preclinical studies (in vivo) of animal testing [21 CFR Part 58(d and e)], and clinical investigations of human subjects (21 CFR Part 812). While planning your testing and evaluation strategy, you should follow Good Laboratory Practice (GLP), Good Clinical Practice (GCP), and the Quality System Regulation. These scientific practices are required by FDA and describe the Agency's expectations for the kind of data quality and integrity they'll want to see in your submission.

Laws moved on to her clinical study overview, "As for clinical studies, medical devices intended for pediatric population might require clinical data to demonstrate safety and probable benefit but in some cases, well-designed bench and animal testing might be sufficient to evaluate the device. It is best to talk with the review division within CDRH regarding this. The amount and type of evidence required will depend on a number of factors, including:

- The nature of the device
- What is already known about the product in the adult population (if relevant)
- The underlying disease or condition being treated
- If what is known in adults can be extrapolated to the pediatric population

Exhibit 3. Suggested Nonclinical and Preclinical Testing for the PHL System

1. **In vitro testing:** Prior to testing, characterize the device based on the materials being used for the PHL System.
   - Specify the device characteristics (e.g., pacing functions, pump performance, materials used and their generic chemical compositions and formulations).
   - Provide documentation to certify all incoming raw materials will conform to specifications to assure that each device produced will have an identical material make-up.
2. **In vivo testing:** Following GLP, test the PHL System on an appropriate animal model for preliminary risk assessment and to gain information on the local and systemic responses to the device. These test results will help justify that the device is safe for future clinical studies in human pediatric patients.
   - Consult FDA for applicable animal models for testing. Choose a model with a test system that will best simulate conditions in a child's body. Juvenile animal models may be the most appropriate as they may correspond better with unique aspects of the target pediatric population's stage of development.
3. **Risk Analysis:** Identify and evaluate all potential predicted risks posed by the device using information from literature, similar devices, FDA's post-market databases, and in vitro testing.
   - Analysis may include Fault Tree and Failure Modes and Effect Analysis (FMEA)*. Identify the probability and severity of each identified hazard. Describe potential mitigation strategies.

**Guidance for Industry, Q9 Quality Risk Management (Published June 2006) http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073511.pdf*

"While extrapolation of data (Appendix C) from adult to adolescents may be possible[8], extrapolation of data from adults to infants or newborns could be very difficult. However, when the course of the disease and the device's effects are similar in adult and pediatric patients, if the adult data are of sufficient quality, the pediatric indication may be supported by the adult data with only limited additional safety data in the pediatric population. When the prognosis, severity, or symptoms of a disease in the adult population are significantly different than in the pediatric population, the device's effects may not be well understood, or there may be risks specific to the pediatric population that make gathering clinical data necessary. For example, downsizing devices to fit pediatric patients may change the physical characteristics of the materials used in the device and pose specific risk to the pediatric population. However, given that your device is unique and there is nothing like it on the market, the extrapolation may be problematic. I would recommend that you discuss this with the review division within CDRH.

"Finally, because weight, body size, and physiologic and neurologic development all vary among pediatric subpopulations and change as the child grows, clinical data may be needed to assess safety and probable benefit in the various subgroups. In some cases, it may be possible to extrapolate from one group to another, thus limiting or removing the need for clinical data for all subgroups. Data from the study of an adult orthopedic implant may be extrapolated to adolescents without the need of an extra trial, but not to infants as their physiology often limits the use of data extrapolation from other populations like children or adolescents. The physical growth of the child may mandate the growth or replacement of a device over time.

"Devices that are already approved and indicated for adult populations may be modified for pediatric uses as well. To support these pediatric modifications, the manufacturer should conduct a risk analysis of the necessary changes and develop methods to adequately address or mitigate the identified associated risks. This may require either verification testing alone, or additional validation testing in the intended pediatric population. For example, downsizing an adult implantable heart pump to fit a child may change the fluid dynamics of the blood flow. Therefore, verification and validation tests using bench and animal models should be performed to ensure specific flow requirements be met.

"A clinical study may also be needed if in vitro and animal tests are insufficient to demonstrate that identified hazards associated with the device have been adequately mitigated. Such a trial may also be warranted if a significantly modified device is needed for the pediatric population. For this study, supplementation from extrapolation also may be appropriate. You, as the sponsor, should comply with 21 CFR 820 Quality System Regulation (cGMP) and GLP to carry out these activities."

Ethical Issues in Pediatric Studies

Wanting more guidance, Marse asked, "What other aspects of pediatric clinical studies do we need to consider?"

"Ethical issues are present in all clinical studies[9] and are of the utmost importance in pediatric studies where there may be additional ethical issues," Laws stated firmly. "Special measures are needed to protect the rights of pediatric study participants and shield them from undue risk. The sponsor is required to provide a framework to ensure that pediatric clinical studies are ethically conducted. There are at least six areas defined under GCP that sponsors are responsible for (Table 4). An objective ethical review committee, the IRB, is necessary to

[8]Regulatory Challenges in Extrapolation of Adult Medical Device Data to Pediatric Populations by Dr. Markham Luke
http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM285293.pdf

[9]ICH E11 pp. 12-14
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073143.pdf

Table 4: Protection of Pediatric Population in Clinical Studies

Sponsor Responsibilities	Description
IRB	The IRB should include members who are knowledgeable in pediatric ethical, clinical, and psychosocial issues
Recruitment	Free from inappropriate inducements either to the parent(s) or legal guardian, or the study participant
Consent	Fully informed consent should be obtained from the legal guardian in accordance with regional laws or regulations
Assent	A child's affirmative agreement to participate in a clinical investigation
Minimizing Risk	Every effort should be made to anticipate and reduce known hazards
Minimizing Distress	Efforts should be made to ensure participants' experiences are positive and to minimize discomfort and distress

review issues related to pediatric studies. Study protocols should be carefully designed to subject participating children to minimum but acceptable risks. The risks and benefits must be transparent and acceptable to both the children and their guardians before the study. A child's participation in a trial must be free from coercion. Fully informed consent should be obtained from the legal guardian in accordance with regional laws or regulations. Furthermore, participants have no obligation to continue the study and will incur no penalty from withdrawing from a study. Pediatric studies should be performed in institutions that provide a child-friendly environment, with child-focused infrastructure and personnel to minimize patient distress.

"Once you've completed these steps and gathered the necessary data for the PHL System, you should be ready to submit your HDE application."

HDE Application Review

"How does the FDA review HDE applications?" Stewarth asked.

"HDE approval is based upon, among other criteria, a determination by FDA that the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. So FDA will review all the preclinical, animal, and clinical data to make their decision," Laws replied. "Once you have collected all of the necessary data and compiled your HDE application, FDA has 75 days from the date of receipt to approve or deny an HDE application (21 CFR Part 814.114).

"Are there any post-approval requirements we need to be concerned about?" asked Marse.

"Yes," said Laws, "there are post-approval requirements which include medical device reporting, updates to ensure that the device still qualifies for HUD designation, HDE status, HDE annual reports, and possibly post-approval studies." (Table 5)

"In addition, once a HUD device is approved and available on the market, its use must still be monitored by an IRB and, if it is labeled for pediatric patients and has been allowed to make profit by FDA, then it will need to undergo an annual safety review by the FDA's Office of Pediatric Therapeutics Advisory Committee. In this case, CDRH presents the safety data to FDA's Pediatric Advisory Committee (PAC). Additionally, you will need to

Table 5. Post-Approval Requirements

Requirement	Description	Regulation
Medical Device Reporting	PHL is responsible for submitting medical device reports to FDA and to the IRB of record whenever a HUD may have caused or contributed to a death or serious injury, or has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.	21 CFR Parts 803.5 and 814..126(a)
HUD Designation	FDA requires updated information on a periodic basis demonstrating that the HUD designation is still valid based on the most current and authoritative information available. PHL, the HDE holder, must report the total number of devices shipped or sold since initial HDE marketing approval.	21 CFR Part 814.126(b)
HDE Status	FDA may withdraw HDE status if the disease or condition affects more than 4,000 individuals in the U.S. per year after the approval, or the agency subsequently approves a PMA or clears a 510(k) for a comparable device with the same indication as the PHL System.	21 CFR Part 814.102

submit an HDE annual report and sometimes there are post approval studies required as conditional of approval."

Laws concluded the meeting. "I know this has been a lot to digest. Feel free to review the information I've provided and contact me if you have any more questions. You can also read the guidance documents and regulations provided by the FDA that we've talked about for more information."

Saturated, yet satisfied they'd received the information they needed to get started, the employees of PHL thanked Dr. Laws' for her guidance.

Moving Forward

When they got back to the office, Versetz went straight to her computer. She had been looking up something on her phone during the entire ride back to the office.

"What are you typing so furiously?" Marse asked while walking to his office.

"I'm contacting the cardiology review division at the FDA for a Pre-Submission meeting," she replied without looking up from her screen.

"Really?!" Marse exclaimed. "My head is still sore from all this regulatory talk! Shouldn't we take a break for a second?"

Smirking, Versetz hit the enter key to send her email before turning to raise an eyebrow at her employers. "Why don't we do a quick run through of what we learned while it's still fresh, and then you can take a break."

"Fine," the men sighed. They headed into Marse's office.

"Okay," Versetz began, "now we have a road map to get our PHL System into the market where it can help children. We know that the dual cardiac pacing and blood pumping function of the PHL System makes it unique and the device can only be used to treat pediatric restrictive cardiomyopathy and that there is no other comparable device available in the health care system that treats or prolongs the lives of the small number of pediatric patients afflicted with restrictive cardiomyopathy. Additionally, we know that this population is small, so the number of people diagnosed annually should be below the 4,000 patient per year limit. This should qualify our device as a HUD. What's next?"

"We have to carefully characterize our targeted pediatric population, fine tune the PHL System design," said Marse.

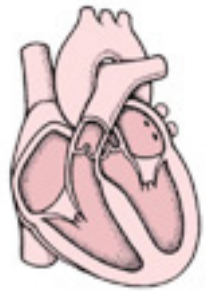
"And we know that the HDE regulatory path we'll follow is very similar to a PMA, but we'll just be exempt from having to demonstrate device effectiveness," Stewarth added. "We still have to demonstrate the PHL System is safe and has probable benefit for the targeted patient population."

"That's right. And we'll get feedback on our proposed study design during our Pre-Submission meeting before we start," Versetz concluded.

Stewath and Marse exchanged smiles. "Sparky," Stewarth said, "it looks like we are finally on our way. I can't wait to see the difference the PHL system will make in the lives of children living with restrictive cardiomyopathy."

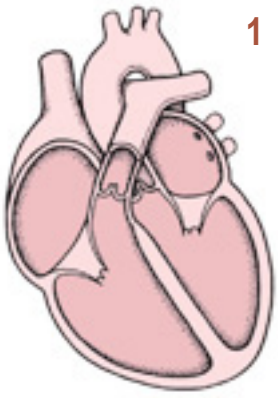
"Well then, gentlemen," Versetz stood and turned to leave the office, "let's get to work!"

APPENDIX A: CARDIOMYOPATHY



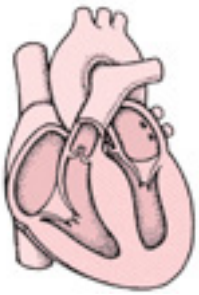
Normal

There are three main types of cardiomyopathy—dilated (1), hypertrophic (2), and restrictive (3). In dilated cardiomyopathy, the ventricles enlarge. In hypertrophic cardiomyopathy, the walls of the ventricles thicken and become stiff. In restrictive cardiomyopathy, the walls of the ventricles become stiff, but not necessarily thickened.



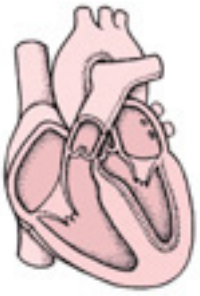
1

Dilated Cardiomyopathy



2

Hypertrophic Cardiomyopathy



3

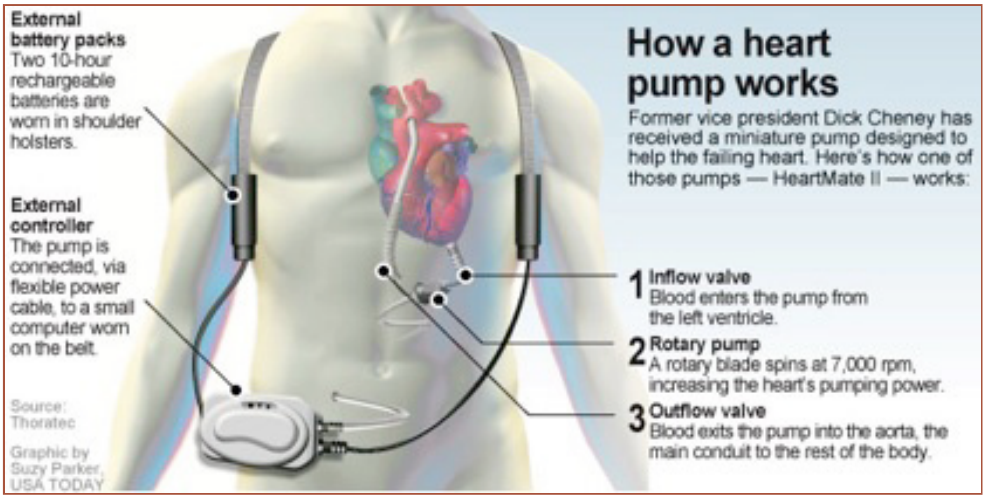
Restrictive Cardiomyopathy

Source: "Types of Cardiomyopathy." Available at: http://www.daviddarling.info/encyclopedia/C/cardiomyopathy.html

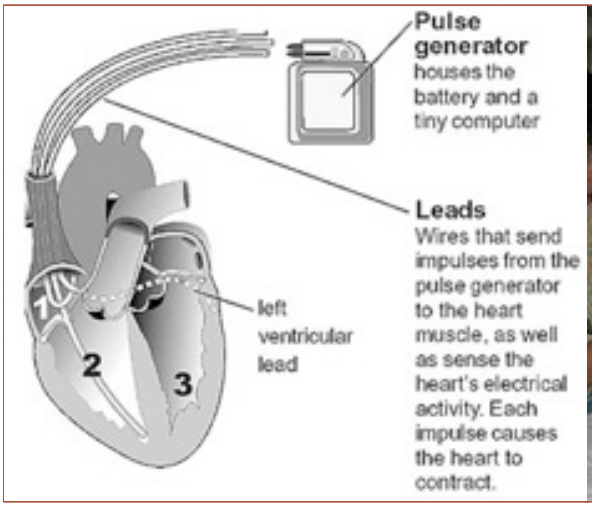
APPENDIX B: THE PHL SYSTEM

The PHL System is a combination of a ventricular assist device (VAD; Image A) and an electrical pacing controller (Image B). One of the main concerns when designing such a system for pediatric patients is patient size and growth while using the device (either until a heart is available for transplant or possibly throughout the rest of a patient's life). Image C shows a cardiac pump designed for pediatric patients.

A



B



C

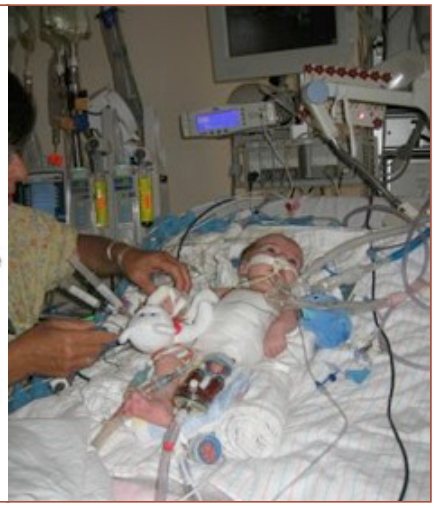


Image sources: Suzy Parker. "How a heart pump works." USA Today. Available at: http://usatoday30.usatoday.com/news/washington/story/2011-08-31/Taciturn-Cheney-cant-stop-talking-about-heart-device/50196688/1

Cleveland Clinic. "Biventricular Pacemaker: CRT Device." Available at: http://my.clevelandclinic.org/heart/services/procedures/biventricular_pm.aspx

Kenny Goldberg. "UC San Diego Engineers Try to Redesign Heart Pump." KPBS. Available at: http://www.kpbs.org/news/2012/nov/13/uc-san-diego-engineers-try-redesign-heart-pump/

APPENDIX C: USING SCIENTIFIC RESEARCH DATA (EXTRAPOLATION) TO SUPPORT PEDIATRIC MEDICAL DEVICES[1]

Design challenges in pediatric clinical studies include small sample sizes and lack of control groups. Recruitment of subjects for pediatric studies is difficult due to the low incidence of disease, ethical concerns of informed consent and assent, and reluctance in participation because of treatment concerns. Parents would like their sick children to receive treatment rather than be part of the control group or placebo without treatment. These various concerns may contribute to challenges in recruiting pediatric patients in research trials, with a subsequent lack of statistical power in study results.

The Pediatric Medical Device Safety and Improvement Act of 2007 (PMDSIA) allows extrapolation of effectiveness data from adults to children, and also across pediatric subpopulations based on valid scientific rationale. It is important to consider potential extrapolation of data from prior clinical studies in adults, because it not only helps to foster pediatric labeling and establish on-label use of approved medical devices in children, but also allows sponsors to make use of all available data and minimize the risks of clinical studies on children.

Sponsors of pediatric studies are encouraged to use valid statistical models for borrowing data from adult (or other pediatric) studies. The Bayesian approach to statistical modeling[2] readily applies to situations where the information from prior studies is relevant to forming conclusion in a current study. This approach allows sponsors to borrow strength (Statistical information) from previous (adult or pediatric) studies to make inferences about the current pediatric population under study. The extent of permitted borrowing depends on the similarity of prior study populations with the current pediatric population. Dissimilarities in biologic or physiologic characteristics, as well as study design differences (e.g., enrollment, informed consent, treatment and handling in the trials) may affect borrowing. The "Guidance for the Use of Bayesian Statistics in Medical Device Studies" (cited above) discusses more requirements in considering the types of prior studies that would be appropriate for borrowing strength in any particular situation. The Bayesian approach may help to overcome some of the challenges of pediatric clinical studies.

[1]*Transcript for Public Workshop - Using Scientific Research Data to Support Pediatric Medical Device Claims, December 5, 2011* *http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm285898.htm*

[2]*Guidance for the Use of Bayesian Statistics in Medical Device Studies* *http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071121.pdf*

GLOSSARY

Annual Distribution Number (ADN): The maximum number of HUD designated devices permitted to be distributed in any calendar year.

The ADN is determined by the FDA when approving the HDE. The ADN is defined as the number of devices "reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States." When determining the ADN, FDA considers the number of devices per year reasonably needed to treat, diagnose, or cure an individual ("first multiplier") and multiplies that value by 4,000 ("second multiplier"). By law, the second multiplier is always 4,000, regardless of whether the target population estimate is fewer than 4,000 individuals. Therefore, the ADN will be equal to or greater than 4,000, depending on the value of the first multiplier.

See section 520(m)(6)(A)(ii) of the Act and section 613(b) of FDASIA for more details.

Approval: Approval of a medical device [or clearance for devices subject to 510(k), see below] must be obtained from the FDA by demonstrating that the device is reasonably safe and effective, and that the benefits outweigh the risks for the intended patient population before it can be put into commerce.

In the case of Humanitarian Use Devices (HUDs) a Humanitarian Device Exemption (HDE) must be obtained. Under an HDE, a sponsor is exempt from the effectiveness requirements. HDE approval is based upon, among other criteria, a determination by FDA that the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

Biocompatibility: The ability of a material to perform with an appropriate host response in a specific application.

Cardiac Pacing: Regulation of the rate of contraction of the heart muscle by an artificial cardiac pacemaker

Cardiomyopathy: Cardiomyopathy is a chronic disease of the heart muscle (myocardium), in which the muscle is abnormally enlarged, thickened, and/or stiffened. The weakened heart muscle loses the ability to pump blood effectively, resulting in irregular heartbeats (arrhythmias) and possibly even heart failure.

Clearance: Clearance of a medical device not exempt from 510(k), and not subject to PMA, must be obtained from the FDA by demonstrating substantial equivalence (SE) to its predicate device(s) before it is put into commerce.

Clinical Investigation (Trial or Study): A systematic investigation conducted to evaluate the safety and effectiveness of a medical device using human subjects or specimens.

Code of Federal Regulation (CFR): The Code of Federal Regulations (CFR) is the codification of the general and permanent rules and regulations (sometimes called administrative law) published in the Federal Register by the executive departments and agencies of the federal government of the United States. The CFR is published by the Office of the Federal Register, an agency of the National Archives and Records Administration (NARA), and is divided into 50 titles that represent broad areas subject to Federal regulation.

Current Good Manufacturing Practices (cGMP): Production and testing practices that help ensure safe, effective, and quality products. In the United States, cGMP Regulations are promulgated by the FDA under the authority of the FD&C Act (Chapter IV for food; Chapter V, Subchapters A, B, C, D, and E, for drugs and devices). The "c" stands for "current", reminding manufacturers that they must employ up-to-date technologies and systems to comply with the regulation. It is the manufacturers' responsibility to be current.

Device Classification: The Food and Drug Administration (FDA) has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. The three classes and the requirements which apply to them are:

Device Class and Regulatory Controls:

1. Class I General Controls
   - With Exemptions
   - Without Exemptions
2. Class II General Controls and Special Controls
   - With Exemptions
   - Without Exemptions
3. Class III General Controls and Premarket Approval

Design Controls: Procedures established to control the design of a medical device in order to ensure that specified design requirements are met. (21 CFR Part 820.30)

Effectiveness: There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use will provide clinically significant results. (21 CFR Part 860.7)

Extrapolation: Inference of a value on the basis of that which is known or has been observed.

Federal Food Drug & Cosmetic (FD&C) Act: This is a set of laws passed by Congress in 1938 giving authority to the FDA to oversee the safety of food, drugs, and cosmetics. The Act has been amended many times, most recently to add requirements about bioterrorism preparations and user fees.

Good Clinical Practices (GCP): A set of guidelines that must be followed when conducting clinical trials to ensure that the rights and well-being of the trial participants are protected and that the data generated in the trial is valid. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials involving human participants. The guidelines were developed in order to provide drug clinical trials with a unified standard across the European Union, Japan, and the United States and were labeled ICH-GCP at the International Conference on Harmonization (ICH), 1996. For medical devices, ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects–Good Clinical Practice was developed and is the global standard for medical device GCP.

Good Laboratory Practices (GLP): A set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported, and archived. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments.

Guidance Documents: Documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Draft guidance documents are for the public to comment on and suggest changes for, but are not for implementation. (See 21 CFR Part 10.115 [b], [d], and [g])

Humanitarian Device Exempting (HDE): To obtain approval for a Humanitarian Use Device (HUD), a Humanitarian Device Exemption (HDE) application is submitted to FDA. An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA.

Humanitarian Use Devices (HUDs): A HUD is a device that is intended to benefit patients with rare diseases by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year.

Examples of HUDs include a fetal bladder stent, iris replacement device, radioactive microspheres for cancer treatment, and semi-constructed finger joints.

Implant: A device placed into a surgically or naturally formed cavity of the human body intended to remain there for a period of 30 days or more. In order to protect public health, FDA may determine that devices placed in subjects for shorter periods are also implants.

In vitro: Outside the living body and in an artificial environment

In vivo: In the living body of a plant or animal

Incidence: Frequency of new cases per year.

Indication for use: The term "Indication for Use" describes the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.

Informed Consent: A process by which a subject voluntarily confirms his or her willingness to participate in a particular investigation after having been informed of all aspects of the investigation relevant to the subject's decision to participate. Documented by means of a written, signed, and dated informed consent form. Informed consent should include elements from 21 CFR Part 50.20.

Institutional Review Board (IRB): A board, committee, or other group formally designated by an institution to review, approve the initiation of, and conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights, safety, and welfare of human subjects. The IRB should be established, operated, and function in conformance with 21 CFR Part 56. The term has the same meaning as "institutional review committee" in section 520(g) of the FD&C Act.

Intended Use/Purpose: Intended use means the general purpose of the device—or what the device does—and encompasses the indications for use. It is the use for which a product, process or service is intended according to the specifications, instructions, and information provided by the manufacturer.

Investigation: A clinical investigation or research involving one or more subjects to determine the safety and/or effectiveness or probable benefit of a device.

Investigational device: An unapproved new device or a currently marketed device being studied for an unapproved use in a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of the device.

Investigational device exemption (IDE): IDE refers to the regulations under 21 CFR Part 812. A regulatory submission to study a medical device in human subjects. IDEs are only required for studies performed in the United States. An IDE allows an investigational device to be used in a clinical study to collect the safety and effectiveness data required for a marketing application. For significant risk device studies, an IDE must be approved by the FDA prior to initiating the study.

Investigator: An individual who conducts a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed to, or used involving a subject. In the event of an investigation being conducted by a team of individuals, "investigator" refers to the responsible leader of that team.

Medical Device: An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

1. Recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them
2. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
3. Intended to affect the structure or any function of the body of man or other animals, and
4. Does not achieve any of its primary intended purposes through chemical action within or on the body of a human or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes (Section 201[h] of the FD&C Act).

Patient Registry: A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.

Premarket Approval (PMA): The FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Any Premarket Approval application for a Class III medical device, including all information submitted with or incorporated by reference therein (21 CFR Part 814.3). Class III devices are those that cannot be classified as Class I or Class II devices because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and either (1) are purported to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health; or (2) present a potential unreasonable risk of illness or injury.

Premarket Notification–510(k) Clearance: Section 510(k) of the FD&C Act requires device manufacturers, who must register, to notify FDA of their intent to market a medical device at least 90 days in advance. This is known as premarket notification—also called PMN or 510(k). This allows FDA to determine whether the device in question is equivalent to a device already placed into Class I, Class II, or Class III requiring 510(k), or a legally marketed preamendment device. Thus, "new" devices (not in commercial distribution prior to May 28, 1976) that have not been classified can be properly identified. Specifically, medical device manufacturers are required to submit a premarket notification if they intend to introduce a device into commercial distribution for the first time or reintroduce a device that will be significantly changed or modified to the extent that its safety or effectiveness could be affected. Such change or modification could relate to the design, material, chemical composition, energy source, manufacturing process, or intended use.

Product Code: The name and product code identify the generic category of a device for FDA. The Product Code assigned to a device is based upon the medical device product classification designated under 21 CFR Parts 862-892.

Probable Benefit: An explanation of why the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Such explanation shall include a description, explanation, or theory of the underlying disease process or condition, and known or postulated mechanism(s) of action of the device in relation to the disease process or condition. [21 CFR Part 814.104(b)(3)]

Quality System Regulation (21 CFR Part 820): Requirements related to the methods used in, and the facilities and controls used for designing, manufacturing, packaging, labeling, storing, installing, and servicing of medical devices intended for human use.

Regulatory Pathways: Before a medical device can be put into the U.S. market, manufacturers of medical devices have to submit evidence to demonstrate product safety and effectiveness to the Office of Device Evaluation (ODE) or to the Office of In Vitro Diagnostic and Radiological Health (OIR) of Center for Devices and Radiological Health (CDRH) at FDA. There are various submission processes and respective applications for evaluation. PMA, PMA Supplement, Product Development Protocol (PDP), Humanitarian Device Exemption (HDE), IDE, IDE Amendment, IDE Supplement, 510(k), and de novo are programs administered by ODE and OIR. They are also called regulatory pathways.

Restrictive Cardiomyopathy: The stiffened heart walls cannot stretch properly to allow enough blood to fill the ventricles between heartbeats. As the stiffening worsens, heart failure occurs. The blood backs up into the blood vessels, causing fluid buildup in tissues (congestion and edema).

Safety: There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use outweigh any probable risks. (21CFR Part 860.7)

Scientific Evidence: Evidence that serves to either support or counter a scientific theory or hypothesis. The strength of scientific evidence is generally based on the results of statistical analysis and the strength of scientific controls. For example, information from well-controlled clinical studies.

Significant and Non-Significant Risk Devices: A "significant risk device" presents a potential for serious risk to the health, safety, or welfare of a subject. These devices are either intended as an implant or are substantially important in diagnosing, curing, mitigating, or treating disease (e.g., dental lasers, embolization devices for urological use, collagen, and bone replacements).

A "non-significant risk device" does not pose a significant risk to the human subjects (e.g., external monitors for insulin reactions, general biliary catheters, MRIs within specified parameters).

Both terms are in respect to their use as investigational devices.

Spirometer: A device that parent and child can use at home to tell if the child will experience an asthma attack. Checking "peak flow" is one of the best ways to control asthma. It can help parents keep the child's asthma from getting worse. Asthma attacks do not usually come on without warning.

Sponsor: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

Sterility: Condition of being aseptic, or free from all living microorganisms.

Transplantation: The grafting of tissues taken from the patient's own body or from another.

Validation: Confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled

Verification: Confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled.

STUDENT ACTIVITIES

SESSION 1

I. Review the following materials before Session 1:

1. Videos

   a. NIH Children and Clinical Studies

   (Approximately 10 minutes)

   http://www.nhlbi.nih.gov/childrenandclinicalstudies/index.php

   b. Children's Cardiomyopathy Foundation

   (Approximately 7 minutes)

   http://www.youtube.com/watch?v=yrBzgpoij30

   c. Cardiovascular System

   (Approximately 1 minute)

   http://www.nlm.nih.gov/medlineplus/ency/anatomyvideos/000023.htm

   d. FDA Patient Safety News Video—FDA-SHOW4-SEG1-Home Monitoring System for Pacemaker

   (Approximately 1 minute)

   http://www.accessdata.fda.gov/cdrh_docs/psn/video/mpeg/FDA-SHOW4-SEG1.MPG

   e. FDA Safety News Video—FDA-SHOW2-SEG3-Pacemaker for Treating Congestive Heart Failure

   (Approximately 1 minute)

   http://www.accessdata.fda.gov/cdrh_docs/psn/video/mpeg/FDA-SHOW2-SEG3.MPG

   f. Cardiac Conduction System

   (Approximately 1 minute)

   http://www.nlm.nih.gov/medlineplus/ency/anatomyvideos/000021.htm

   g. Arrhythmias

   (Approximately 1 minute)

   http://www.nlm.nih.gov/medlineplus/ency/anatomyvideos/000005.htm

2. Mandatory Reading

Note: A Draft Guidance is subject to change and is not for implementation.

   a. Premarket Assessment of Pediatric Medical Devices

   http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089742.pdf

b. Humanitarian Device Exemption (HDE): Questions and Answers—Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff

http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm389154.htm

c. Humanitarian Use Device (HUD) Designations

http://www.fda.gov/downloads/ForIndustry/DevelopingProductsForRareDiseasesConditions/DesignatingHumanitarianUseDevicesHUDS/LegislationRelatingtoHUDsHDEs/UCM336515.pdf

3. Optional Reading

Note: A Draft Guidance is subject to change and is not for implementation.

a. FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigation

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf

b. Guidance on IDE Policies and Procedures

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf

c. Information on Premarket Approval (PMA)

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm

II. Answer the following questions before Session 1—Fundamental Concepts:

1. Describe the indications for use of the PHL System.

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073945.pdf

2. Justify why the HDE application is the appropriate regulatory pathway for the PHL System.

http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/hdeapprovals/default.htm

III. Additional References

1. The Federal Food Drug & Cosmetic (FD&C) Act

http://www.fda.gov/Regulatory Information/Legislation/FederalFood Drugand Cosmetic ActFDCAct/default.htm

2. Sub Chapter II—Definitions § 321. Definitions [p. 32, paragraph(h)]

http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapII-sec321.pdf

SESSION 2

I. Review the following materials before Session 2:

1. CDRH Learn Videos

a. Overview of Medical Device Regulations

(Approximately 31 minutes)

http://fda.yorkcast.com/webcast/Viewer/?peid=040308365ec8405bad39b06de8561bdc1d

b. Good Clinical Practice 101: An Introduction

(Approximately 29 minutes)

http://fda.yorkcast.com/webcast/Viewer/?peid=477af877491747379c36c4ab1c7421b9

c. The Sponsor: Responsibilities in Medical Device Clinical Trials

(Approximately 17 minutes)

http://fda.yorkcast.com/webcast/Viewer/?peid=88f92205e9624bbea1d627126af5360f

d. The Clinical Investigator: Responsibilities in Medical Device Trials

(Approximately 14 minutes)

http://fda.yorkcast.com/webcast/Viewer/?peid=29b55c1dd3f64d8fa74ca2227df14b39

2. Mandatory Reading

a. ICH E6 Good Clinical Practice: Consolidated Guidance

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf

3. Optional Review and Readings

a. 21 CFR 820: Quality System Regulation (CGMP) Video (up to slide 48 of 86)

(Approximately 2 hours)

http://fda.yorkcast.com/webcast/Viewer/?peid=dd2d4823b14a4e4ca6d60eae43c5ac9c

b. Quality System Information for Certain Premarket Application Reviews

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070899.pdf

c. Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems (p. 1-39)

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071986.pdf

II. Questions for in-class discussion:

1. What have you learned from the case study about the requirements of an HDE application?
   a. Prerequisites
   b. Justification for an HDE submission
   c. Data extrapolation
2. Discuss the types of nonclinical testing or studies that should be addressed for the PHL System.
   a. Nonclinical in vitro tests
   b. Preclinical in vivo tests
3. What have you learned from the case study about the following aspects of Good Clinical Practices (GCP)?
   a. Human subject protection
4. Explain the roles and responsibilities of those involved in clinical investigations.

III. Additional References

1. FDA Good Laboratory Practices

   http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133765.pdf

2. 21 CFR Part 58—Good Laboratory Practices

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58&showFR=1

3. 21 CFR Part 820 Preamble—Quality System Regulation

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820&showFR=1

SESSION 3: STUDENT PROJECT AND PRESENTATION

I. Review the following materials before beginning the project:

1. HDE Approval Information of a Pediatric Ventricular Assist Device (VAD)—H100004

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=H100004

2. HDE Approval Information of a Child Left Ventricular Assist System—H030003

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=H030003

3. PMA Approval Information of a Ventricular Assist Device—P060040

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P060040

II. Answer the following questions for the team project:

1. Explain the challenges of marketing pediatric medical devices. Suggest ways to overcome these challenges.
2. What are the ethical concerns of pediatric clinical trials?
3. Would you use data from other studies in the PHL System HDE application? Justify your decision. (Refer to Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials, p. 17-19)

   http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071121.pdf
4. What are the scientific and regulatory challenges both the FDA and industry must consider when using data to extrapolate or establish probable benefit for the pediatric population?

   http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM285293.pdf
5. Describe how you would carry out the clinical investigations of PHL System. Explain the ways that you would protect the subjects of your studies.
   a. Refer to ICH E6 Good Clinical Practice: Consolidated Guidance (p. 1-38)

      http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf
   b. ICH E11 Clinical Investigation of Medicinal Products in the Pediatric Population (p.12-14)

      http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073143.pdf
6. Prepare an outline detailing an HDE submission for the PHL System.

   Refer to Case Study Exhibit 2 and Table 4, and the HDE Checklist

   http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/ucm056830.pdf

III. Additional References

Note: A Draft Guidance is subject to change and is not for implementation.

1. FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigation

   http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf
2. Information on Premarket Approval (PMA)

   http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm
3. HUD Designations Guidance

   http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm336515.pdf
4. Humanitarian Device Exemption (HDE): Questions and Answers – Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff

   http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm389154.htm
5. Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff Guidance

   http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf